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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,599	05/31/2005	Joseph M. Penninger	SONN:064US/10416096	8087
33425 7590 06/01/2009 FULBRIGHT & JAWORSKI L.L.P. 600 CONGRESS AVE. SUITE 2400 AUSTIN, TX 78701				
EXAMINER SAIDHA, TEKCHAND				
ART UNIT		PAPER NUMBER		
1652				
MAIL DATE		DELIVERY MODE		
06/01/2009		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/518,599

Applicant(s)

PENNINGER ET AL.

Examiner

Tekchand Saidha

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 67, 68, 73, 100-102, 104-107, 110, 116-120 and 125 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 67, 68, 73, 100-102, 104-107, 110, 116-120 and 125 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

Final Rejection

1. During a telephone interview with Applicant's representative Mr. Travis M. Wohlers on May 20, 2009, allowable subject matter was discussed. Mr. Wohlers agreed to delete the word 'therapeutically' from claim 67. However, subsequent examination of the application indicated that issues still remain and addressed in this Office Action. Any inconvenience caused by this action is regretted.
2. Amendment filed on 3/12/2009, in reply to Non-Final Office Action mailed 12/15/2008 is acknowledged.
3. Claims 67-68, 73, 100-102, 104-107, 110, 116-120 & 125 are present and under consideration in this application.
4. Applicant's arguments filed 3/12/2009 have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).
5. Any objection or rejection of record not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.
6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67-68, 73, 100-102, 104-107, 110, 116-120 & 125 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ

1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claim 67 is drawn to a method of treating an ACE2 decreased state comprising administering to a mammal having cardiovascular disease ~~hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis~~, renal failure, and/or lung disease a therapeutically effective amount of an ACE2 polypeptide. Claim 68 limits the mammal of claim 67 to include human. Claim 73 limits the method to include co administration of ACE2 polypeptide and ACE inhibitor. Subsequent claims limit the method to include mammal that has lung disease subsequently limiting to respiratory lung and lung cancer respectively. It is also noted that claims 104 & 110 further limits the lung disease to include genus of other lung condition including chronic obstructive pulmonary disease, pneumonia, asthma, chronic bronchitis, pulmonary emphysema, cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary embolism, pulmonary sarcoidosis, tuberculosis, or lung edema. Claims 105-107 limit the method of claim 67 to include ACE2 polypeptide is mouse, rat or human ACE2 polypeptide. Claims 116-120 limits the method genus claims to treating cardiovascular disease such as chronic heart failure and myocardial infarction, hypertension, etc. Claims 125 limits the method claim to kidney disease being treated. The aspects considered broad are: the breadth of subject population, any

method of administration to affect genus of disease associated with ACE2 decreased state by ACE2 polypeptide.

It is noted that as recited, claimed invention reads on a broad genera of protein therapy. Specific considerations for *in vivo* protein therapy includes effective protein production at the target site have to be addressed for an *in vivo* method of treating ACE2 decreased state in a mammal. Although Applicant's specification teaches role of ACE2 is a critical negative regulator of heart contractility and heart function in a ACE2 knockout mouse model, however, the specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in any mammal, (ii) the claimed method would have resulted in providing the ACE2 in deficient cells in amount sufficient to treat genus of diseases associated with ACE2 decreased state by administering ACE2 polypeptide to any site. As will be shown below, these broad aspects as well as limitations were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The invention describes compositions and methods for use in diagnosing and treating heart, lung and kidney diseases, including hypertension, coronary heart disease, heart and kidney failure, lung edema, and lung injury such as in toxic shock or artificial ventilation (pp 1). The specification contemplates new paradigm for the regulation of the renin-angiotensin system and shows a completely new and unexpected usage of ACE2 (page 2). Pages 2-7 broadly summarize the invention and provide a brief description of figures. Pages 7-31 provide a detailed description of preferred embodiments, therapeutic methods, screening of ACE2 activator, knockout mammals kits, definition of terms, and other therapeutic aspects of ACE2 and characterization of ACE2 as a negative regulator of RAS and its role in blood pressure control. Pages 31-44 describe specific example showing studies in ACE2 knockout mice and mapping of ACE2 to QTL on the X-chromosome in hypertensive rat strains. It is

noted that instant specification describes ACE2 mapping to a QTL on the X-Chromosome in three hypertensive rat strains, it is noted that ACE2 in mouse and rat is predominantly expressed in kidney and heart, with little expression in lung and liver (see Figure 1c and example). The specification also exemplified that ACE2 protein expression was markedly reduced in SBH/y animals that are fed a normal diet, while an increase in blood pressure of SBH/y rats following a 4-week diet of DOCA-salt correlated with further decreased ACE2 protein expression (see Figure 2B). It is emphasized that specification describes that in order to test whether ACE2 has any essential role in the cardiovascular physiology and the pathogenesis cardiovascular diseases, the mouse ACE2 gene was cloned and an ACE2 knockout mouse was made (see example and Figure 3a-c). It is noted that loss of ACE2 had no apparent direct effect on blood pressure homeostasis in this defined mouse background however backcross with mutant mice to other mouse backgrounds show the role of ACE2 in blood pressure control similar to human (see example and Figure 4). The western blot of kidney of these ace2 deficient mice show enhanced expression of hypoxia inducible factor-1alpha (HIF1-.alpha.) and vascular endothelial growth factor (VEGF). The examples further describe specific phenotype of this knockout mice showing slight wall thinning of the left ventricle and increased chamber dimensions (see Figure 5) and anterior left ventricular wall (AW) and increase in the left ventricle end diastolic dimension. It further characterizes that ACE2 functions as a negative regulator of the RAS and controlling endogenous levels of AngII. Using double knock out specification shows that ablation of ACE expression on an ace2 mutant background completely abolished the heart failure phenotype of ace2 single knockout mice (see figure 8a-c). Specification describes that ACE2 knockout mice showed a significantly more severe response in lung elastance than wild type mice. Thus, specification contemplates the significance of ACE2 in protecting lungs from acute acid-induced injury (see example, pages 40-43). However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that any protein could be delivered in any cell of any mammal at therapeutic effective levels. The art of protein therapy and their

delivery at the time of the filing of this application was unpredictable wherein protein is expressed in an individual suffering from cardiovascular or lung disorder.

The specification does not disclose the effectiveness of the method of the instant invention in treating any ACE2 decreases state. Nor does it teach the effectiveness of the method in increasing the level of ACE2 in any cell and reversal of any pathology or condition associated with decreased ACE2 state. The specification only teaches role of ACE2, but fails to disclose any method in treating any condition by administering any composition of ACE2. The specification teaches only the role of ACE2 in the heart failure, hypertension and lung pathology, but fails to disclose the efficacy of using said any method wherein administering a ACE2 composition resulted in the treatment of any disorder. The examples in the specification do not disclose a therapeutic effect in any patient after therapy with any composition and/or treating with any composition. Although working examples are not required, particularly in predictable art, the presence or absence of working example is one of the factors that must be considered, particularly in the unpredictable arts. In the absence of specific guidance, one of ordinary skill in the art would be required to engage in undue experimentation to make and use the invention as claimed.

It is emphasized that the mechanism of development of each disease is different, the parameters of treating any particular disease associated with ACE2 decreased state such as heart failure may be different, from those used in treating another disease such as lung cancer and therefore, the reversal of the symptoms in one case due to any therapy can not be predictive of the effects in another. Such parameters will include the site of action of the protein, cell types and tissues affected by the ACE2 deficiency. In the instant case, specification has exemplified most of its finding in a ACE2 knockout mice. The specification teaches the different phenotype of ACE2 knockout mice and ACE/ACE2 double knockout mice. Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618) state that single genes are often essential in a number of different physiological processes. Hence deletion of an individual gene in the instant case ACE2 may prove so drastic or so widespread as to create an amalgam of phenotypes whose

interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene. Thus, the specification at best provide some evidence of role of ACE2 deficiency in hypertension and lung disorders using a transgenic knock out mice, but these findings could not be predictive of any method of treating any condition by delivering a nucleic acid or ACE2 protein. It is noted that claims as recited and the specification is silent about whether a nucleic acid encoding ACE2 protein or ACE2 polypeptide would be in active form when administered via any route at any site as broadly recited in rejected claims. Therefore, these molecules may not even act as an activator. It is also noted decreased ACE2 decreased state include plurality of cardiac disorder including atherosclerosis. Prior to instant invention, Tailleux et al (2003) describe that lipid and lipoprotein metabolism is dissimilar between mice and humans. In addition, the regulations of genes encoding proteins that are involved in lipid and lipoprotein metabolism are not identical between humans and mice and thus data obtained in the mouse are not always directly relevant to humans. Third, the mouse is highly resistant to atherosclerosis and does not develop atherosclerotic lesions spontaneously. Tailleux et al further teach, "homologous recombination technology allows the extinction of a specific gene (knockout). However, in such mouse models, the functionality of all metabolic pathways is not necessarily maintained, and thus the model only provides information about whether a ligand requires the presence of the deleted gene. However, in most murine models created by genetic modification, lipoprotein levels are insufficiently altered to induce the development of atherosclerotic lesions. Thus, in absence of any direct evidence in the specification or prior art it would be difficult to predict the role of administering ACE2 activator. Thus, at the time of filing, the resulting phenotype of a knockout was considered unpredictable. Furthermore, contrary to applicants findings, prior art teaches a method of treating an ACE-2 associated state in humans suffering from a blood pressure related disorder, such as congestive heart

failure by administering a therapeutically effective amount of an ACE-2 inhibiting compound, such that the ACE-2 associated state is treated (Acton et al US Patent no 6,632,830). Furthermore, Acton et al contemplate administering an effective amount of an ACE-2 inhibiting compound and an effective amount of an ACE inhibitor to treat cardiac conditions which is contrary to the teaching of instant application that intend to treat same conditions by administering ACE2 activator (see column 3, lines 54-67 bridging to column 4). Therefore, the observations of Acton et al in the prior art and the stand taken that phenotypes disclosed in the instant application cannot be solely due to loss of ACE2 gene. It is apparent that in absence of any specific showing that administering Ace2 polypeptide would results in result in any therapeutic effect, an artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of the art of treating cardiac or lungs condition by administering ACE2 activator showed conflicting results and was not completely resolved at the time of filing of this application.

The specification also contemplates delivering polypeptides to any cells using *in vivo* delivery vehicles such as but not exclusive to liposomes. In summary, specification does not specifically provide any specifics in term of what and where the therapeutic composition would be administered for an optimal therapeutic response, it is noted that, there are art-recognized limitations of using liposome and there is no teaching or contemplation as to how an artisan of skill would have addressed these limitations. For example, Filion et al (Br J Pharmacol. 1997;122(3): 551-557) listed several adverse effects associated with cationic lipids or cationic liposome (table 2, pp 18) such as immunomodulation of animals, complement activation, induction of pulmonary inflammation and toxicity. The specification does not provide any guidance as to what doses of the cationic lipid would be used in the method without eliciting adverse effects. It is noted that the prior art at the time of filing of this application did not provide any guidance in this regard either. Davis et al (Current Opinion in Biotechnology 2002, 13:128-131) evinces an optimistic outlook for non-viral delivery system but states "perfect system does not currently exist". Davis et al describe problems associated with

non-viral delivery system, which includes obstacles in manufacturing, toxicity, formulation and stability.

With regards to evaluation of efficacy of a therapeutic protein, dosing, clearance and efficacy of the product, preclinical evaluation for toxicity and immunogenicity are important steps. It is noted that toxicity with proteins often presents differently than with small-molecule pharmaceutical drugs (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 3, paragraph 1). Further, immunogenic responses in patients can be triggered by large-molecules products, product-related or process-related impurities raising unwanted antibodies. Additionally, the way in which unwanted immunogenicity may present in different patients is unpredictable and varied, even with identical amino acid sequences; immunogenicity to the product can vary dramatically (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 4-5). Thus, preclinical evaluation for efficacy and immunogenicity of a therapeutic protein is vital for the development of therapeutic protein. It is noted that, it is important to assess the half-life and clearance of the protein as the terminal elimination half-life of related products can vary drastically. For example, six companies manufacture FDA-approved versions of human growth hormone, with the same number of amino acid and very similar molecular weights, presented terminal half-life from 1.75 to 10 hours. Thus, such large variations can impact the effectiveness of the product and the as the body's immune response to it (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 5, paragraph 1). Hence, the risk of immunogenicity should be assessed for each product and characterized with appropriate therapeutic response. In the instant case, specification provides no guidance of administering any polypeptide for the treatment of any condition associated with ACE decreased state. A reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification as filed. Without sufficient guidance, the mere enumeration of treatment of genus of diseases associated with decreased ACE2 state in any mammal is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. With regards to evaluation of a therapeutic protein, dosing, clearance and

efficacy of the product, Prior art teaches that preclinical evaluation for immunogenicity are important steps. The specification contemplates administration of **soluble rhACE2** from a specific source, in a manner that increases the level of ACE2 by direct administration; however, the specification fails to teach any immunogenicity or efficacy of any such composition in any mammal because of said administration. Hence, one skill in the Art at the time of the invention could not reasonably predict that the use of Ace2 protein therapy will treat any condition associated with ACE2 decreased state in any mammal.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of *in vivo* delivery of any ACE2 activator such that it transduces cells sufficiently to elicit a pharmacological response for a desired duration in any tissue of any mammal suffering from any condition associated with decreased ACE2 state. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of gene and protein therapy and *in vivo* delivery and treatment of any condition associated with ACE2 decreased state in general by gene and protein delivery *in vivo* was unpredictable at the time of filing of this application as supported by the observations in the art record.

New Arguments:

All the evidence presented by the Applicants to confirm their enablement requirement is post filing, either in the form of Dr. Schuster's or Dr. N. Nue's Declaration(s) or the work of Imai et al. There is no data or evidence present in the instant application as filed, which demonstrate to one of skill in the art what a therapeutically effective amount of ACE2 polypeptide is? The difference in Applicants' and Examiner's arguments appears to be the 'therapeutic component' and the specificity of the method. A **therapeutically** effective amount of **soluble rhACE2** from a specific source (not ACE2 from any source) that has been used for treatment – amounts to a 'cure', and the invention is not enabled for such a claim. No treatment

method of any of the diseases is supported by the instant specification to have resulted in a cure.

Further, the post filing declarations of Drs. Neu and Schuster present data showing actual administration of the ACE2 which is supported with standard techniques presented in the specification as filed. The specification as filed does not provide evidence in support of enablement. The rejection is therefore maintained.

Applicants' arguments are essentially a repeat of previous arguments and do not overcome the rejection for all the reasons of record.

7. ***Claim Rejections - 35 USC § 112*** (second paragraph)

Claims 67-68, 73, 100-102, 104-107, 110, 116-120 & 125 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: For claim 67 a step to determine the 'decreased state of ACE-2' will be important to know how much of the ACE-2 level is required or is considered as at a level that would require administration of ACE2 polypeptide? It would be important to clarify what level of ACE-2 is considered 'ACE-2 decreased state' and with reference to which disease. Is there a marker to determine such a control?

Applicants argue that current claim 67 recites that the ACE2 decreased state is a cardiovascular disease, renal failure, and/or lung disease. Claim 67 also recites the step of identifying a mammal having cardiovascular disease, renal failure, and/or lung disease. This identification is sufficient to identify the ACE2 decreased state because hypertension, as well as other cardiac, lung, and kidney diseases are associated with an ACE2 decreased state (see e.g., p. 2, ln. 28 to p. 3, ln. 6). The involvement of ACE2 in these diseases is related to its role as a negative regulator in the renin-angiotensin system (RAS) (see Specification, paragraph spanning pages 2-3). The RAS is a regulator of blood pressure homeostasis (Specification, p. 1, ln. 21-22). The enzyme ACE cleaves AngI to AngII, which can contribute to hypertension by promoting vascular smooth muscle vasoconstriction and renal tubule sodium reabsorption (Specification, p. 1, ln. 23-27). ACE2, on the other hand, decreases AngII signaling because ACE2 cleaves AngI to AngI-9 and AngII to AngI-7 (Specification, p. 2, ln. 5-9; p. 29, ln. 8-16).

Thus, ACE2 can be used to treat cardiovascular disease, renal failure, and lung disease, which are associated with vascular smooth muscle vasoconstriction and/or renal tubule sodium re-absorption.

Furthermore, determining the level of ACE2 in a subject prior to treatment is unnecessary. This is evident from the animal model studies in which mice with severe acute lung injury (see Neu Declaration, para. 14); pigs with ARDS (see Neu Declaration, para. 11; Schuster Declaration, para. 17-37); pigs with pulmonary hypertension (Schuster Declaration, para. 14); mice with cardiovascular disease (Schuster Declaration, para. 13-14); and mice with kidney disease (Schuster Declaration, para. 15-16), were all treated for their respective disease without first having the ACE2 level determined.

Applicants arguments are considered but not found to be persuasive because without determination of the starting level of 'ACE decreased state in a mammal', one would not know how much of the ACE-2 level is to be raised to treat a disease or is considered as at a level that would require administration of ACE2 polypeptide? It would also be important to clarify what level of ACE-2 is considered 'ACE-2 decreased state' and with reference to which disease. The rejection is therefore maintained.

8. Claim 125 recites the limitation "Kidney disease" in claim 67. There is insufficient antecedent basis for this limitation in the claim.

9. ***New Rejection***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 67-68, 73, 100-102, 104-107, 110, 116-120 & 125 are rejected under 35 U.S.C. 102(e) as being anticipated by Acton et al. (USP 6,194,556, filed December 11, 1997, previously cited).

Claim 67 is drawn to a method of treating an ACE2 decreased state comprising administering to a mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease a therapeutically effective amount of an ACE2 polypeptide. Claim 68 limits the mammal of claim 67 to include human. Claim 73 limits the method to include co administration of ACE2 polypeptide and ACE inhibitor. Subsequent claims limit the method to include mammal that has lung disease subsequently limiting to respiratory lung and lung cancer respectively. It is also noted that claims 104 & 110 further limits the lung disease to include genus of other lung condition including chronic obstructive pulmonary disease, pneumonia, asthma, chronic bronchitis, pulmonary emphysema, cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary embolism, pulmonary sacrodosis, tuberculosis, or lung edema. Claims 105-107 limit the method of claim 67 to include ACE2 polypeptide is mouse, rat or human ACE2 polypeptide. Claims 116-120 limits the method genus claims to treating cardiovascular disease such as chronic heart failure and myocardial infarction, hypertension, etc. Claims 125 limits the method claim to kidney disease. The aspects considered broad are: the breadth of subject population, any method of administration to affect genus of disease associated with ACE2 decreased state by ACE2 polypeptide.

Acton et al. teach a method of treating diseases or disorders which are associated with aberrant ACE-2 level or activity (see column 7, lines 39-42), by administering ACE-2 therapeutics, ACE-2 agonist or ACE-2 antagonist (see columns 9-12). Column 11, lines 25-26 define ACE-2 therapeutics as various forms of ACE-2 polypeptides. Figures 2-3 compares the amino acid sequence homologies of **ACE-2** from **mouse, rat and human among other**.

ACE-2 agonist is defined in a preferred embodiment as ACE-2 proteins or derivatives thereof which mimic at least one ACE-2 activity. (see column 39, lines 39-42). Further evidence that the ACE-2 agonist used herein includes the ACE-e polypeptides can be found through out the specification.

The term aberrant activity is defined as ACE-2 activity that is weaker or stronger than the native or wild-type polypeptide (see column 12, lines 26-38) and therefore considered equivalent to ACE2 decreased or increased state.

These ACE-agonists or ACE-2 proteins or ACE-therapeutics or ACE-antagonist are use for the treatment of various diseases such as hypertension, Congestive heart failure (CHF), inflammatory reactions and methods to reduce pain (see column 7, lines 42-46, column 10, lines 55-60), pulmonary or lung diseases among others (columns 1-2) ; and kinder disease (see 58, lines 43-57).

The reference further provides methods for determining whether a subject has or is likely to develop hypertension, hypotension or congestive heart failure, for example, comprising determining the level of an ACE-2 gene or protein, an ACE-2 bioactivity and/or the presence of a mutation or particular **polymorphic variant** in the ACE-2 gene. Detection is accomplished via determining whether a subject has an abnormal mRNA and/or protein level of ACE-2, such as by **Northern blot analysis**, reverse transcription-polymerase chain reaction (RT-PCR), in situ hybridization, immunoprecipitation, **Western blot hybridization**, or immunohistochemistry. According to the method, cells are obtained from a subject and the ACE-2 protein or mRNA level is determined and compared to the level of ACE-2 protein or mRNA level in a healthy subject. An abnormal level of ACE-2 polypeptide or MRNA level is likely to be indicative of an aberrant ACE-2 activity (see column 44, lines 54-67 --to-- column 45, lines 1-11 & lines 12-67, for example).

The reference anticipates for teaching all the claim limitations.

Applicants argue that "For a publication to anticipate a claim under 35 U.S.C. § 102 it must not only disclose all elements of the claim within the four comers of the document, but must also disclose those elements "arranged as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). The Action, however, has not identified any disclosure in Acton that even suggests using ACE2 to treat cardiovascular, lung, and/or kidney disease. Rather, the Action merely cites to disclosures in Acton of various conditions and of various ACE2 therapeutics (ACE2

agonists or ACE2 antagonists) without any regard for which conditions Acton states could be treated with either an ACE2 agonist or antagonist."

Applicants further argue that "As explained on page 2 of the Specification and in previous responses, Acton predicted that ACE2 functioned to hydrolyze AngI into AngII, which is a vasoconstrictor, based on its homology to ACE (Acton, col. 56, ln. 19-39). Accordingly, Acton predicted that ACE2 antagonists would be useful in treating hypertension and congestive heart failure (Id.; see also col. 7, ln. 47-51; col. 57, ln. 10-20). In other words, Acton incorrectly predicted a function for ACE2 that was the opposite of what it was later demonstrated to be. It appears that the only therapeutic uses of an ACE2 agonist contemplated by Acton were for the treatment of inflammation, burns, and insect bites (Acton, col. 58, ln. 7, ln. 51-54). The Action's mixing and matching of disparate teachings in Acton is legally flawed. See e.g., 545 F.3d at 1369."

Applicants arguments are considered but not found to be persuasive because while the sequence and arrangement are important factors in the case cited "*Net MoneyIN, Inc. v. VeriSign, Inc.*", 545 F.3d 1359, 1369 (Fed. Cir. 2008)", it relevance does not appear to be significant in the instant biotechnology case having a distinct fact pattern, compared to the cited case dealing with "claim directed to system for processing credit card transactions over Internet".

As pointed out in the 102 rejection, the Acton reference does teach all the claim limitations and one of ordinary skill in the art would recognize that the cited art anticipates the claims as explained in the rejection. The rejection is therefore maintained.

10. **Conclusion**

No Claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on (571) 272 0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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May 29, 2009